IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: R. Zeman
CONTAG et al.	Group Art Unit: 1645
Serial No.: 08/844,336	Confirmation No.: 7227
Filing Date: April 18, 1997	Customer No.: 20855
Title: BIODETECTORS TARGETED TO SPECIFIC LIGANDS	

REPLY BRIEF

Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This Reply Brief is filed in response to the Examiner's Answer mailed September 9, 2011. Accordingly, this Reply Brief is timely filed.

REAL PARTY IN INTEREST

The real party in interest is Xenogen Corporation, assignee of the instant application, as recorded in the USPTO at Reel 9497, Frame 0636 on October 6, 1998.

RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences.

STATUS OF CLAIMS

Pending: claims 1, 5, 6, 9, 21, 22 and 25 to 27

Canceled: claims 2-4, 7, 8, 10-20, 23 and 24

Appealed: claims 1, 5, 6, 9, 21, 22 and 25 to 27

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether, pursuant to 35 U.S.C. § 112, 1st paragraph, the specification provides adequate written description for the subject matter of claims 1, 5, 6, 21, 22 and 25 to 27.

ARGUMENTS

A. The claims are fully described by the as filed specification

Claims 1, 5, 6, 21-22 and 25-27 remain rejected under 35 U.S.C. § 112, 1st paragraph as allegedly not adequately described by the as-filed specification. (Examiner's Answer, pages 4-9). In particular, it was again alleged that the claims encompass "limitless combinations" that have not been shown to work as biodetectors and that only the exemplified biodetectors (using PhoQ and PhoP) are actually described. *Id.*

For the reasons of record, Appellants reiterate that that the as-filed specification amply describes the claimed subject matter.

1. Each element is clearly described by the as-filed specification

It remains the case that the as-filed specification clearly describes the claimed subject matter, namely a biodetector made up of:

(i) a transmembrane fusion protein made up of an antibody (extracellular portion) and a kinase (intracellular portion);

(ii) a transducer that is activated by the kinase; and

(iii) a responsive element coupled to a gene that produces light, in which the activated transducer binds to the responsive element and causes expression of light-producing gene.

Each and every one of these elements is clearly described by the as-filed specification and in light of the teachings of the state of the art at the time of filing.

First and foremost, the specification provides detailed description of the specified components of the transmembrane fusion protein, namely an extracellular antibody component and an intracellular kinase. *See,* page 6, lines 7-16; page 8, lines 13-20; page 11, lines 30-31; page 12, lines 4-9; page 14, lines 21-29; page 15, lines 24-28, emphasis added:

> However, currently-available biosensors are limited to the detection of those molecules for which an endogenous bacterial receptor exists. In contrast, the present invention enables the generation of biosensors selective for any antigen or substance which can be selectively recognized by an antibody or receptor. Specifically, the present invention combines the selectivity of ligand-specific binding and the versatility of the antibody repertoire with the sensitivity of bioluminescent detection, employing entities that specifically respond with photon emission to predetermined ligands. The approach of the present invention thus permits the generation of extremely sensitive biodetectors for the development of a wide variety of assays detecting any number of commercially important molecules. ...
>
> The present invention is directed to targeted ligand-specific biodetectors for detecting and monitoring selected substances, including microorganisms and their products/by-products, chemical compounds, molecules, arid ions, for a wide range of applications. In a preferred embodiment, the biodetectors of the present invention combine the specificity and selectivity of ligand-specific binding with the sensitivity of

bioluminescent detection by employing entities that specifically respond to the binding of a predetermined ligand with photon emission. Thus, the approach of the present invention permits the generation of sensitive biodetectors for the development of a wide variety of assays detecting and monitoring **any** selected substance. ...

Once bound to a ligand, an enzymatic cascade is activated that serves to transmit the signal. ...

Furthermore, as the ligand-specific domain of the signal converting element of the biodetector system may be exchanged like a cassette, an unlimited number of biodetectors can be generated to recognize any desired or selected substance. Thus, the biodetectors of the present invention provide a flexible, generic system that can be adapted to recognize any selected substance, out of a wide variety of choices. Biodetectors targeting a substance of interest can rapidly be developed.

The signal converting element is composed of an "extracellular" portion selectively binding a specific substance and an "intracellular" portion capable of activating the transducer. Typically, the signal converting element will be a transmembrane fusion protein composed of an extracellular ligand-binding portion, *e.g.*, an antibody and an intracellular enzymatic portion, which is activated upon binding of the extracellular portion to a selected target. Accordingly, the signal converting element is designed to convert the recognizing and binding of a specific substance, *i.e.*, ligand into an intracellular signal, resulting in the activation of the transducer component, which in turn activates a promoter that drives the expression of the reporter protein. ...

...The signal transforming domain may consist of an enzyme or active domain of an enzyme that has any number of protein modifying functions which may include phosphorylation, dephosphorylation, methylation, acetylation and protease activity. Such enzymes include protein kinases, phosphorylases, protein methylases, acetylases, proteases, proteinase K, serine proteases, among others. ...

In addition, the state of the art as summarized in the specification, clearly evidences that the claimed antibody-kinase transmembrane fusion proteins and their role in initiating a signal transduction cascade were known (see, page 26, line 25 to page 27, line 18 of the as-filed specification, emphasis added):

> The fusion protein composed of an antibody heavy chain and a surface protein known to transduce signals for gene regulation, and a promoter that is affected by this signal is placed in front of the marker gene. Antibody light chains are coexpressed in the biodetector to provide additional ligand specificity (Borrebaeck et al., 1992, *Biotechnology* 10:697-698). Bacterial phosphatase has been selected as the initial transmembrane and signal-transducing component of the gene fusion **because of its current use** in identifying surface expressed fusion proteins in bacteria (Kohl et al. 1990, *Nucleic Acids Res.* 18:1069; Weiss and Orfanoudakis, 1994; *J. Biotechnol.* 33:43-53) and a colorimetric substrate is available for measuring phosphastase activity. **Antibody fragment-phosphastase fusions have been generated with retention of both ligand binding specificity and phosphatase activity** (Kohl et al. 1991, *Acad. Sci.* 646:106-114; Wels *et al.,* 1992, *Biotechnology* 10:1128-1132). **Phosphastase-antibody fusions have been used to generate labeled antibodies for immunoassay** (Carrier *et al.,* 1995, *J. Immunol. Methods* 181:177-186; Ducancel *et al.,* 1993, *Biotechnology* 11:601-605; Weiss *et al.*, 1994; *J. Biotechnol.* 33:43-53; Weiss and Orfanoudakis, 1994; *J. Biotechnol.* 33:43-53; Wels *et al.,* 1992, *Biotechnology* 10:1128-1132). In additional antibodies to modified bacterial phosphatase have been shown to alter phosphatase function [citation omitted], indicating that protein-protein interactions can modulate phosphatase activity most likely through conformational changes in the phosphatase molecule. Expression of phosphatase fusion proteins on bacterial cell surfaces transduces a signal, phosphorylation into the cell which induces expression of specific genes. This system may be modified to tightly link the expression of marker proteins, luciferase and its accessory proteins, to binding of the ligand to the antibody-phosphatase fusion protein, *i.e.,* a ligand-dependent molecular switch.

Plainly, the as-filed specification, in light of the state of the art at the time of filing, describes how antibody-kinase transmembrane fusion proteins function to initiate an intracellular cascade to induce expression of specific genes.

Appellants were clearly also in possession of the second element of the claimed biodetector, namely a transducer that is activated by the kinase component of the transmembrane fusion protein. *See, e.g.,* page 16, lines 11 to 22 of the as-filed specification:

3. Transducers

The transducer is activated by the signal converting element upon ligand binding. The transducer may be any molecule that can recognize and respond to a change in conformation, electrical charge, addition or subtraction of ay chemical subgroup such as phosphorylation, glycosylation, and in turn is capable of triggering a detectable response.

In specific embodiments of the invention, activation of the transducer triggers, directly or indirectly, the activation of a transcription activating element, *e.g.,* a promoter, to effect the activation of a reporter gene or reporter operon. Transcription and translation of the reporter gene or operon in turn results in a gene product or gene products which produces a detectable signal, such as light. ...

Furthermore, as noted above, the specification and art clearly teach that antibody-kinase transmembrane fusion proteins initiate a signal cascade, including via a transducer in the intracellular portion. *See, e.g.,* page 27, lines 2-18:

...Antibody fragment-phosphastase fusions have been generated with retention of both ligand binding specificity and phosphatase activity (Kohl et al. 1991, *Acad. Sci.* 646:106-114; Wels *et al.,* 1992, *Biotechnology* 10:1128-1132). Phosphastase-antibody fusions have been used to generate labeled antibodies for immunoassay (Carrier *et al.,* 1995, *J. Immunol. Methods* 181:177-186; Ducancel *et al.,* 1993, *Biotechnology* 11:601-605; Weiss *et al.*, 1994; *J. Biotechnol.* 33:43-53; Weiss and Orfanoudakis, 1994; *J. Biotechnol.* 33:43-53; Wels *et al.,* 1992, *Biotechnology* 10:1128-1132). In additional antibodies to modified bacterial phosphatase have been shown to alter phosphatase function [citation omitted], indicating that protein-protein interactions can modulate phosphatase activity most likely through conformational changes in the phosphatase molecule. Expression of phosphatase fusion proteins on bacterial cell surfaces **transduces** a signal, phosphorylation into the cell which **induces expression** of specific genes. This system may be modified to tightly link the expression of marker proteins, luciferase and its accessory proteins, to binding of the ligand to the antibody-phosphatase fusion protein, *i.e.,* a ligand-dependent molecular switch.

Thus, kinase-responsive transducers are clearly described by the as-filed specification.

Finally, the as-filed specification also describes, in detail, light-producing reporter genes that are activated by the transducer (via the antibody-kinase fusion protein). *See, e.g.,* page 16, line 22 to page 19, line 5.

Thus, the as-filed specification, in view of the state of the art at the time of filing, clearly evinces that Appellants were in possession of the claimed biodetectors, which can include a wide variety of antibody components that bind to any selected substance and initiate a cascade via a kinase (which activates a transducer) that results in a detectable light signal (from any light-generating protein) when the ligand is bound to the extracellular antibody domain.

Moreover, although an applicant is never limited to the exemplified embodiments, it is noted that the working examples provide exemplification of a transmembrane domain comprising an antibody heavy chain and a kinase domain, which kinase activates a transducer which in turn produces a detectable light signal from a luciferase gene. Therefore, the assertion that the "single functional embodiment" uses only bacterial elements and promoters in its bacterial sensor is in error. *See,* Examiner's Answer, page 7. The antibody component is a eukaryotic component that is described in the specification (and art) used as claimed, namely in a fusion protein with a kinase.

2. The specification and art describes the correlation between the claimed structures and their functions

The specification also clearly provides the correlation between structure and function required to satisfy the written description requirement. As detailed above, the specification describes the structure of each component of the claimed biodetectors (*i.e.,* an antibody-kinase transmembrane fusion, a transducer, and a light producing reporter). Any combination of these amply described elements that would produce a functional biodetector would be clear to the skilled artisan. Indeed, as described above, antibody-kinase transmembrane fusion proteins that initiate a cascade resulting in expression of a marker gene were known in the art. Any antibody could be used in combination with a transducer that is activated by a kinase and which transducer in turn induces expression of a light-generating protein.

Simply put, Appellants do not only teach a method of obtaining the claimed biodetectors, they disclose the correlation between the structure and function of each and every element of the claimed biodetectors. Specifically, each of the three components is amply described by structure (antibody-kinase fusion, kinase activated transducer, light-generating protein expressed by kinase activated transducer) and in terms of the nexus between the recited structures and their functions, *i.e.,* the transmembrane domain initiates signal cascade that results in expression of a light-generating protein via the transducer.

Furthermore, Appellants also amply describe that which is new, *i.e.,* biodetectors as claimed using known transmembrane protein cascades. Thus, clear description is present in the original claims and specification, and the written description requirement has therefore been satisfied. Appellants have shown possession of the claimed subject matter at the time of filing – clearly and unmistakably. As a result, the rejection cannot be sustained.

3. The case law supports a finding of adequate description based on the particular facts and claims

It remains the case that the written description requirement is satisfied if reading the disclosure in light of the knowledge possessed by the skilled artisan at the time of filing, for example as established by reference to patents and publications available to the public prior to the filing date of the application, shows possession of the claimed subject matter. See, e.g., *In re Lange*, 209 USPQ 288 (CCPA 1981); *Falkner v. Inglis*, 79 USPQ2d 1001 (Fed. Cir. 2006); *Capon v. Eshhar* 76 USPQ2d. 1078 (Fed. Cir. 2005). Moreover, although working examples of multiple representative species are also never required to show possession, the case on appeal includes such examples. *Id.* See, e.g., *In re Lange*, 209 USPQ 288 (CCPA 1981). Thus, the Examiner has not met his burden of establishing why a skilled artisan would not have recognized that the applicant was in possession of claimed invention at the time of filing. *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim,* 191 USPQ 90 (CCPA 1976).

Additional case law relevant to the instant Appeal includes *Capon v. Esshar* 76 USPQ2d. 1078 (Fed. Cir. 2005), in which the Federal Circuit held that the precise sequence of a chimeric antibody need **not** be described because the components were well known (*Capon* at page 1085, emphasis added):

> The "written description" requirement must be applied in the context of the particular invention and the state of the knowledge. The Board's rule that the nucleotide sequences of the chimeric genes must be fully presented, although the nucleotide sequences of the component DNA are known, is an inappropriate generalization. ...
>
> The "written description" requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution.

Thus, Capon, in which the Federal Circuit held that the precise sequence of a chimeric antibody need **not** be described because the components were well known, is directly relevant to the pending case. As in *Capon*, the claimed antibody and kinase components of the chimeric transmembrane fusion protein (which initiates a signal-transduction cascade intracellular) are also well known.

In *Union Oil v. Atlantic Richfield*, the Federal Circuit made clear that the specification need **not** describe the exact chemical composition of every claimed combination, adding that neither the Patent Act nor case law requires such detailed disclosure (*see, Union Oil* at 1233):

> Appellant refiners assert that the specification does not describe the exact chemical component of each combination that falls within the range claims of the '393 patent. However, neither the Patent Act nor the case law of this court requires such detailed disclosure. ...
>
> The inquiry for adequate written description simply does not depend on a particular claim format, but rather on whether the patent's description would show those of ordinary skill in the ... art that the inventors possessed the claimed invention at the time of filing.

In *Falkner,* the Federal Circuit reaffirmed that working examples are not required to satisfy the written description requirement, even for a broad genus (*see, Falkner,* 1004):

> Specifically, we hold, in accordance with our prior case law, that (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

With particular regard to recitation of known structures, the Federal Circuit cited *Capon* in reaffirming that adequate written description does not require re-description of the sequence of known molecules and that literature available at the time of filing must be considered in determining the adequacy of the written description (*Falkner, Id.*):

> Indeed, a requirement that patentees recite known DNA structures, if one existed, would serve no goal of the written description requirement. It would neither enforce the quid pro quo between the patentee and the public by forcing the disclosure of new information, nor would it be necessary to demonstrate to a person of ordinary skill in the art that the patentee was in possession of the claimed invention. As we stated in Capon, "[t]he 'written description' requirement states that the patentee must describe the invention; it does not state that every invention must be described in the same way. As each field evolves, the balance also evolves between what is known and what is added by each inventive contribution." Id. at 1358. Indeed, the forced recitation of known sequences in patent disclosures would only add unnecessary bulk to the specification. Accordingly we hold that where, as in this case, accessible literature sources clearly provided, as of the relevant date, genes and their nucleotide sequences (here "essential genes"), satisfaction of the written description requirement does not require either the recitation or incorporation by reference (wherein permitted) of such genes and sequences.

The holding in *Falkner,* like the holdings in *Union Oil, Capon* (and the case law regarding written description generally), provides further support that the written

description rejection in the case on appeal is unsustainable in view of the specification as a whole and the state of the art as exemplified by the literature of record.

It is further noted that the facts in the cases cited by the Examiner, namely *Enzo Biochem Inc. v. Gen-Probe Inc.* 63 USPQ2d 1609 (CAFC 2002) and *University of Rochester v. G.D. Searle & Co.* 358 F.3d 916, 60 USPQ2d 1886 (CAFC 2004) are not relevant to the case on appeal. In *Enzo,* the Federal Circuit addressed whether a deposit of a particular sequence satisfied the written description requirement with regard to certain claims. In *University of Rochester*, the claims at issue were directed to methods for selectively inhibiting PGHS-2 activity in a human host by administering a non-steroidal compound. In this case, the specification did not identify any non-steroidal compounds as recited in the claims. Accordingly, the Federal Circuit found no written description because the compound was entirely hypothetical. This is completely different than the case on appeal and, in fact, the Federal Circuit in *University of Rochester* was clear in noting that written description does not require an actual reduction to practice (exemplification). *See, University of Rochester,* 358 F.3d 916, 926 (Fed. Cir. 2004)

> We of course do not mean to suggest that the written description requirement can be satisfied only by providing a description of an actual reduction to practice. Constructive reduction to practice is an established method of disclosure, but the application must nonetheless "describe the claimed subject matter in terms that establish that [the applicant] was in possession of the . . . claimed invention, including all of the elements and limitations." [citing *Hyatt v. Boone*, 146 F.3d 1348, 1353 (Fed. Cir. 1998)]

Therefore, when properly applied, the case law makes clear that the Examiner errs in asserting that the skilled artisan would not know how to combine <u>any</u> antibody and a kinase into a transmembrane fusion protein and use this transmembrane protein in conjunction with a transducer that is activated by the kinase and light-generating reporter as set forth in the claims. In fact, in view of the clear description in the specification and art, the use of such proteins in signal-transduction cascades was known, it is clear that Appellants were in possession of the claimed subject matter at the time of filing.

In light of these clear teachings of the Federal Circuit, the Office's assertion, in the case on appeal, that Appellants are required to disclose multiple examples of particular biodetectors is inconsistent with the requirements of the first paragraph of Section 112. Indeed, Examples 9 and 14 of the PTO Guidelines on Written Description clearly state that disclosure of a single representative species can adequately describe a broad genus, where, as in this case, the specification and state of the art show an applicant was in possession of the claimed subject matter. These Examples were favorably commented on by the Federal Circuit in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 63 USPQ2d 1609 (Fed. Cir. 2002).

Similarly, the Examiner's assertion that prokaryotic components cannot be combined with eukaryotic components contradicts both the description in the specification (in which eukaryotic antibody components are clearly combined with bacterial components to in functional biodetectors) and the state of the art at the time of filing. The written description requirement of Section 112 does not necessitate that Appellants exemplify all possible embodiments (including embodiments that can be empirically determined). Rather, the relevant inquiry is whether the as-filed specification, in light of the state of the art, shows that Appellants were in possession of the claimed subject matter at the time of filing.

For the reasons of record, it is clear that, in view of the state of the art regarding fusion proteins involved in cascades and the as-filed specification's clear disclosure in this regard, Appellants have shown possession of the claimed subject matter.

B. Additional arguments regarding dependent claims

For the reasons detailed above with regard to independent claim 1, all the claims are fully described by the as-filed specification. The dependent claims are addressed individually below.

Claims 5, 6 and 27

Claim 5 depends from claim 1 and further specifies that the light-generating protein is a bioluminescent or fluorescent protein, as clearly described, for example on

page 17, line 9 to page 19, line 5 and Examples 4-6. Claim 6 depends from claim 5 and further specifies that the bioluminescent protein is encoded by a luciferase operon. *See, e.g.*, at page 11, lines 15-18; page 17, line 18 through page 19, line 5; Figure 4; and Examples 4-6. Claim 27 depends from claim 5 and further specifies that the light-generating protein is a bioluminescent protein (specification, e.g., at page 16, lines 24-25; page 17, line 18 through page 19, line 5). Thus, the as-filed specification clearly evinces possession of the subject matter of claims 5, 6 and 27.

Claim 9

Claim 9 depends from claim 6 and further specifies that the selected substance is selected from the group consisting of microorganism, virus, retrovirus, protein, sugar and ion. The subject matter of claim 9 is described in detail in the as-filed specification, for example at page 9, lines 1-4; page 15, lines 1-3; and page 23, lines 2-29. Thus, the rejection of this claim cannot be sustained.

Claims 21 and 25

Claim 21 depends from claim 1 and further specifies that the intracellular enzymatic signal transforming domain is a PhoQ intracellular enzymatic domain. Claim 25 depends from claim 1 and further indicates that the intracellular enzymatic signal transforming domain comprises an active domain of PhoQ. As the subject matter is clearly described and exemplified (*see, e.g.,* specification, *e.g.*, at page 15, lines 29-30; Example 2), the as-filed specification evinces possession of the subject matter of claims 21 and 25.

Claim 22

Claim 22 depends from claim 1 and recites a genetically engineered bacterial cell comprising a biodetector according to claim 1, as described for instance on page 8, lines 27-29; page 11, lines 4-18 of the as-filed specification. Thus, the rejection cannot be sustained.

Claim 26

Claim 26 depends from claim 1 and further indicates that that the transmembrane fusion protein is a fusion of an active domain of PhoQ, and a region of a heavy chain antibody, as described for instance at page 15, lines 29-30; page 26, line 25 to page 27, line 18 of the as-filed specification. Thus, the as-filed specification evinces possession of the subject matter of claim 26.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are patentable. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: November 2, 2011

By: _____
Dahna S. Pasternak
Registration No. 41,411
Attorney for Appellants

ROBINS & PASTERNAK LLP
1731 Embarcadero Road, Suite 230
Palo Alto, CA 94303
Telephone: (650) 493-3400
Facsimile: (650) 493-3440

CLAIMS APPENDIX

The claims on appeal are as follows:

1. A biodetector for the detection of a selected substance comprising:

(a) a transmembrane fusion protein comprising an extracellular ligand-specific moiety and a protein-modifying membrane intracellular enzymatic signal transforming domain, wherein the extracellular ligand-specific moiety comprises an antibody and wherein the antibody binds the selected substance, which binding activates the intracellular enzymatic signal transforming domain, wherein the membrane intracellular enzymatic signal transforming domain is a kinase;

(b) a transducer protein, wherein the transducer has an inactive form and an active form which are distinct from each other, and the activated intracellular enzymatic signal transforming domain converts the inactive form of the transducer into the active form of the transducer protein, wherein the transducer and the intracellular enzymatic signal transforming domain are separate proteins;

(c) a responsive element comprising a nucleic acid encoding a light-generating protein operably linked to a transcription activation element, wherein the responsive element is bound by and activated by the active form of the transducer, resulting in a detectable light signal.

5. The biodetector of claim 1, wherein the light-generating protein is a bioluminescent or fluorescent protein.

6. The biodetector of claim 5, wherein the nucleic acid comprises a luciferase operon.

9. The biodetector of claim 6, wherein the selected substance is selected from the group consisting of microorganism, virus, retrovirus, protein, sugar and ion.

21. The biodetector of claim 1, wherein the intracellular enzymatic signal transforming domain is a PhoQ intracellular enzymatic domain.

22. A genetically engineered bacterial cell comprising a biodetector according to claim 1.

25. The biodetector of claim 1, wherein the intracellular enzymatic signal transforming domain comprises an active domain of PhoQ.

26. The biodetector of claim 1, wherein the transmembrane fusion protein is a fusion of an active domain of PhoQ, and a region of a heavy chain antibody.

27. The biodetector of claim 5, wherein the light-generating protein is a bioluminescent protein.

EVIDENCE APPENDIX

No documents are submitted in the Evidence Appendix.

RELATED PROCEEDINGS APPENDIX

As noted above, Appellants are not aware of any related interferences or decisions on appeal. Accordingly, no documents are submitted with this Appendix.